REMARKS

FORMAL MATTERS:

Claims 48-99 are pending after entry of the amendments set forth herein.

Claims 48, 63, and 84 are amended to recite an implantable convective delivery system. Support for these amendments is found in Applicants' specification at page 18, last line of the first complete paragraph, for example. New dependent claims 92-99, reciting sufentanil as the fentanyl congener, have been added. Support for these amendments is found in Applicants' specification at page 7, second paragraph, for example.

No new matter has been added.

DOUBLE PATENTING REJECTION

Claims 48-91 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of co-pending Application No. 11/044,521. Although Applicants do not acquiesce to the propriety of this rejection, in the interest of advancing prosecution, a Terminal Disclaimer is attached hereto, thereby rendering this rejection moot.

REJECTIONS UNDER §103

Claims 48-91 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Magruder et al. (U.S. Patent No. 5,057,318) (hereinafter "Magruder") combined with Athayde et al. (U.S. Patent No. 5,672,167) (hereinafter "Athayde"). This rejection is respectfully traversed.

The Office characterized Magruder as follows:

> US '318 teaches implantable osmotic drug delivery devices that can be highly loaded of beneficial agents and able to deliver active beneficial agents at a controlled rate continuously over time and over a broad range of dosage delivery rates according to predetermined time release pattern (abstract; col.3, lines 20-26, 30-34, 39-42; col.19, lines 27-30; col. 20, lines 20, 34). Example of the drugs suitable for delivery by the implantable osmotic device is analgesic (col.13, lines 60-61).

Office Action at page 5.

The Office recognized that Magruder does not disclose fentanyl, doses, and periods of delivery as presently claimed. The Office asserted that Magruder provides motivation "to use the implantable osmotic device to deliver analgesics that need continuous delivery and [to] manipulate the amount of analgesic and its period of delivery according to the specific patient need." *Ibid.*

In an effort to remedy the deficiency of Magruder, the Office cited Athayde. The Office asserted that

> US '167 teaches osmotic drug delivery device that permits patients with certain medical conditions such as pain to have steady delivery rate of medication to achieve the desired therapeutic effects (abstract; col. 6, lines 31-36). The device enables therapy with highly potent drugs such as fentanyl. The reference teaches that the volume of the drug and the total time to deliver this volume will vary depending on the drug (col.12, lines 49-65; col.13, line 5).

Office Action at pages 5-6.

The Office alleged that, therefore, it would have been obvious to use fentanyl in the implantable device of Magruder "to deliver analgesics at a controlled rate continuously over time and over a broad range of dosage delivery rates according to [a] predetermined time release pattern...," and would have been motivated to do so by Magruder.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference

teachings so as to arrive at the claimed method. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest, all the claim limitations (MPEP § 2143). The teaching or suggestion to arrive at the claimed method and the reasonable expectation of success must both be found explicitly or implicitly in the prior art, or be based on an *explanation* of the knowledge of one of ordinary skill in the art, but cannot be based on Applicant's disclosure (MPEP § 2143 citing with favor, *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991)). *See also, Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 80 USPQ2d 1641 (Fed. Cir. 2006).

All three criteria must be satisfied. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established. In the instant case, the Office has failed to establish a *prima facie* case of obviousness here for at least the following reasons:

First, there would have been no motivation to combine the Magruder and Athayde documents absent Applicants' disclosure. The Magruder device is implantable, but the Athayde device is not. The Office has implied that fentanyl may be used with either type of device. However, there would have been no expectation that fentanyl or a fentanyl congener could have been used in an implantable device as recited in the present claims.

As pointed out by the Examiner, Magruder discloses classes of drugs for delivery at column 13, lines 60-61. However, the Examiner failed to point out that the very next paragraph of Magruder lists representative beneficial agents that can be administered by the Magruder delivery system:

> Representative beneficial agent 20 that can be administered by delivery system 10 include pharmacologically active peptides and proteins, anabolic hormones, growth promoting hormones, hormones related to the endocrine system comprising porcine growth promoting hormone, bovine growth promoting hormone, equine growth promoting hormone, ovine growth pro-

moting hormone, human growth promoting hormone, growth promoting hormones derived by extraction and concentration from pituitary and hypothalmus glands, growth promoting hormones produced by recombinant DNA methods, bovine growth promoting hormone as described in *Nucleic Acid Res.*, Vol. 10, p 7197 (1982), ovine growth promoting hormone as described in *Arch. Biochem. Biophys.*, Vol. 156, p 493 (1973), and porcine growth promoting hormone as described in DNA. Vol. 2, pp 37, 45, (1983). The polyepoxide also comprise growth hormone, somatropin, somatotropin, somatotropin analogues, modified porcine somatotropin, modified bovine somatotropin, derivatives of both porcine and bovine somatotropin, somatomedin-C, gonadotropic releasing hormone, follicle stimulating hormone, luteinizing hormone, LH-RH, growth hormone releasing factor, gonadotropin releasing factor, insulin, colchicine, chorionic gonadotropin, oxytocin, somatotropin plus an amino acid, vasopressin, adrenocorticotrophic hormone, epidermal growth factor, prolactin, somatostatin, somatotropin plus a protein, cosyntropin, lypressin, polypeptides such as thyrotropin releasing hormone, thyroid stimulating hormone, secretin, pancreozymin, enkephalin, glucagon, endocrine agents secreted internally and distributed in an animal by way of the bloodstream, and the like. The beneficial agents and their dosage unit amounts are known to the prior art in *The Pharmacological Basis of Therapeutics*, by Gilman, Goodman, Rall and Murad, 7th Ed., (1985) published by MacMillan Publishing Co., N.Y.; in *Pharmaceutical Sciences*, Remington, 17th Ed. (1985) published by Mack Publishing Co., Easton, Pa., and in U.S. Pat. No. 4,526,938. Generally, the delivery system 10 comprises from about 5 nanograms to 20 grams of beneficial agent 20.

Magruder at column 13, line 62 to column 14, line 36.

The latter passage provides more specific guidance regarding the types of compounds covered under the broad disclosure at column 13, lines 60-61. The passage cited by the Office would be read together with the passage that follows it. The latter passage teaches away from an expectation that any and all members of these classes of agents, analgesic agents for example, would be suitable for use in the Magruder delivery system. Most of the representative beneficial agents are peptides or proteins, such as hormones. For example, colchicine is mentioned specifically at column 14, lines 18-19. Colchicine has been used to relieve pain associated with gout. Colchicine is an alkaloid that is structurally completely different from fentanyl and congeners of fentanyl.

Therefore, the mere fact that analgesics are disclosed generally would not cause one to expect any analgesic, or fentanyl and its congeners in particular, to be suitable for use with

Magruder's implantable device. Any motivation to select fentanyl or its congeners must come from Applicants' specification. As such, the motivation represents impermissible hindsight.

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130 (Fed. Cir. 1994). Once again, only Applicants' disclosure would provide the guidance to use fentanyl in an implantable convective delivery system.

Second, Applicants' invention permits the delivery of high concentrations of fentanyl or fentanyl congener. In the fields of pharmacology and pain management at the time of applicants' priority date, no highly concentrated fentanyl/fentanyl congener formulation was available nor was there any reasonable belief or expectation that one could be attained. As disclosed in Applicants' specification, fentanyl/fentanyl congener formulations having a concentration that is substantially higher than conventional formulations have been invented by applicants, wherein the active agent can be present in up to 10,000 times or greater than the solubility of the fentanyl or fentanyl congener in aqueous solution.[1]

Applicants' ability to produce such formulations provided exceptional benefit to the art in that now, methods of pain management can be carried out by administering exceptionally small volumes of the fentanyl/fentanyl congener formulation to a site, avoiding accumulation of excessive drug at the delivery site (pooling or depot effect) since the rate of administration is at or only slightly higher than the rate of removal of the drug from the delivery site.[2]

The claimed invention is not simply about manipulating delivery volumes and concentration of drug. Rather, the claims, by virtue of the recited delivery rates and administration periods, require use of a *concentrated* formulation of fentanyl or fentanyl congener. As the Office recognizes, these are *highly potent drugs*. Where a highly potent drug such as fentanyl or a fentanyl congener such as sufentanil is to be administered, use of a highly concentrated formulation is not obvious -- especially in the context of an implanted device.

---

[1] See applicants' specification at page 18, second full paragraph through page 21, first full paragraph, and pages 35 and 36.

[2] See applicants specification at page 24, bottom paragraph.

Instead, the natural impulse for a medical practitioner would be to use a dilute formulation containing the highly potent drug. There is simply no teaching, motivation, or suggestion in Magruder or Athayde to use a highly concentrated formulation of a highly potent drug such as fentanyl or a fentanyl congener. Any such motivation must come from Applicants' specification, and therefore represents impermissible hindsight. This may be seen readily by examining the passage of Athayde cited by the Office, reproduced below:

> Because the devices described in the present invention are small and simple, they are particularly suitable for delivering small infusate volumes to the patient. For example, such a device might be sized to contain an infusate volume of from 1 to 20 ml, and to deliver this volume over a period of from 2 hours to 7 days. (The specific volume of infusate contained and total time for delivery would vary depending on the choice of infusate, and would not necessarily be restricted to these quantities.) Thus, the invention enables therapy involving highly potent substances, such as peptide drugs of various kinds, heparin and insulin, analgesics and anesthetics, corticosteroids, immunosuppressants, antineoplastics, antibacterials, and antidotes to chemical or biological poisons and the like, to be administered without subjecting the patient to repeated injections or requiring immobilization of the patient with continuous intravenous therapy.
>
> A number of drug are particularly suited for delivery via the instant infusion device including but not limited to
>
> heparin, insulin, chemotherapeutic agents such as fluorouracil, cisplatin, antibiotics such as adriamycin, oncovin, bleomycin, vancomycin, tobramycin, antinauseants such as haldol, benadryl, antivirals such as gancyclovir, and analgesics such as morphine, codeine, fentanyl, ketorolac, dilaudid and the like.

The volumes and delivery periods in the above passage are expressed as a broad range. Analgesics are not the only type of drug listed. One would not reasonably expect all the volumes and delivery periods to be suitable for all the drugs listed.

As Applicants have pointed out previously, the methods of claims 48-99 require the delivery of an exceptionally small volume of a composition containing the fentanyl/fentanyl congener active agent, yet effective analgesia is achieved in the subject. Delivering such small volumes of drug is counter-intuitive and as such would not be considered by the routineer as part of an optimization protocol, since logically it would be expected that the pharmacological effect of the drug would drop off quickly and become negligible well before one reached the low volume rate delivery as required by Applicants' claims.

Therefore, only Applicants' specification would guide one to pick and choose from Athayde the volumes and concentrations employed by Applicants for use with fentanyl. Accordingly, such picking and choosing represents impermissible hindsight.

Third, there is absolutely no disclosure of sufentanil in the cited documents. Therefore, all the elements of claims 92-99 are neither taught nor suggested by the combination of documents.

Withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number DURE-007CON2.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 19, 2006 By: _____
Richard A. Schwartz, Ph.D.
Registration No. 48,105

Date: December 19, 2006 By: _____
Carol L. Francis, Ph.D.
Registration No. 36,513

Enclosure(s): Terminal Disclaimer of USSN 11/044,521

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231